Commentary on "Brain Environment Interactions: Stress, Posttraumatic Stress Disorder, and the Need for a Postmortem Brain Collection"

Neuropathology of Stress: Prospects and Caveats

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Osuch et al. (this issue) eloquently present the major "knowns" and "unknowns" of brain involvement in stress–related disorders. They describe the contribution and limitations of clinical and preclinical stress research, and offer to establish a "stress dedicated" brain bank that could bridge and integrate information obtained from diverse research modalities. Recent advances in neuropathology enable the study of cellular architecture, neurotransmitters and receptors, signal transduction systems, candidate genes, protein and mRNA expression and much more. However, to prove beneficial, data collection should be done within a well–formulated conceptual framework. Neuropathology has the potential to advance our understanding of the adaptive and pathological effects of stress on the brain. It may help establish a biologically meaningful diagnosis of PTSD and define boundaries and subdivisions of this disorder, as has been done in other neuropsychiatric disorders.

DIVERSITY IN PHENOMENOLOGY OF THE STRESS RESPONSE

Stress is an often used and very broad term, applied to external and internal stimuli that may alter the physical and mental homeostasis (Chrousos and Gold, 1992). Contrary to the initial emphasis on physical threat (Selye, 1936), psychological and experiential difficulties are among the most powerful stressors. Psychosocial, interpersonal, novelty, reward, and anticipation are potent activators of physiological stress systems (Mason, 1975). Research on the relations between specific stressors and specific psychological outcomes found little evidence for the notion that particular risk factors are uniquely related to particular outcomes (McMahon et al., 2003). This heterogeneity in stressors and variability in response to trauma indicates a complex interaction between genetic vulnerability and environment.

The "trauma severity" (A1) criterion of PTSD (American Psychiatric Association, 1994) requires that the traumatic event "involve actual or threatened death or serious injury, or a threat to the physical integrity of self or others," and that "the person's response involved intense fear, helplessness, or horror." Diagnosis of PTSD therefore calls for severe, physical integrity–related stressors. Many of the stressors listed above would not meet this requirement. Still, such seemingly

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commonplace stressors have been linked with the onset of major depression (Kendler, Warkowsky, and Prescott, 1999) and schizophrenia (Corcoran et al., 2003). PTSD may be therefore considered an "exclusion" diagnosis, representing only a small part of stress-related psychopathology.

Epidemiological research disclosed that up to 90% of citizens in the United States are exposed to at least one traumatic event, as defined above, in the course of their lives (Breslau and Kessler, 2001), while many more are exposed to more than one traumatic event. A typical pattern of mental, emotional and physical response is observed after exposure to trauma (Breslau and Kessler, 2001; Foa, Riggs, and Gershuny, 1995; Freedman et al., 1999; Kessler et al., 1995; Rothbaum and Foa, 1993; Shalev et al., 1998). In most people, severity of the response will diminish within days or weeks of exposure. Among those who remain symptomatic, some will go on to chronic PTSD while others may still improve. Certain people develop full-blown PTSD from exposure to apparently minor trauma, while others do not exhibit symptoms even after enduring extreme stress. Some patients with chronic PTSD appear to have a relapsing–remitting course, while others remain invariably symptomatic. Furthermore, many trauma survivors report disturbing symptoms that are clearly the outcome of exposure to the traumatic event but do not meet criteria for PTSD. These are probably more abundant than patients who meet full criteria for the disorder.

This heterogeneity in the response to stress at once demonstrates the limitation in current classification and the need for a neurobiologically based categorization. The diverse phenomenology of the stress response further highlights the potential difficulties in collecting a homogenous patient sample amenable to neuropathological research. If judiciously performed, postmortem brain research could determine if the diversity in the response to stress reflects a continuum of brain histopathological changes or discrete, qualitatively different, brain processes.

NON SPECIFICITY OF STRESS RELATED NEUROBIOLOGICAL FINDINGS

The neurobiological findings in PTSD, as reviewed by Osuch et al., may also not be unique to this disorder and/or may often be difficult to interpret. Reduced hippocampal volume, arguably the most consistent brain–imaging finding in PTSD, has also been reported in other major psychiatric disorders (Beyer and Krishnan, 2002; Callicott, 2003; Hull, 2002; MacQueen et al., 2003; Seidman et al., 2003). Moreover, it is not known if this is a trait phenomenon, preceding trauma and conferring vulnerability (Gilbertson et al., 2002) or a consequence of the traumatic event and/or the ensuing distress (Bremner, 2001). Limbic and prefrontal metabolism deficits, assumed to be closely involved in the neurocircuitry of PTSD, are not consistently demonstrated in imaging studies (Bremner et al., 1999; Liberzon et al., 1999; Shin et al., 1999). Hypothalamic–pituitary–adrenal abnormalities may or may not be present (Raison and Miller, 2003). Fear conditioning may be enhanced (Orr, Metzger, and Pitman, 2002), impaired (Grillon 2002) or unaffected. Cognitive impairment is not robust, and, if present, reflects either prefrontal or hippocampal dysfunction (Danckwerts and Leathem, 2003). This variability in neurobiological attributes of PTSD should alert potential researchers to the difficulties they may encounter in investigating postmortem data.

Evaluation of the genetic contribution in PTSD is equally challenging. It is much simpler in disorders with pure Mendelian inheritance (i.e., Huntington Chorea). The overall inheritability of anxiety disorders is estimated at 30% (Uhl and Grow, 2004), virtually all of which is complex. This prevalence rate probably also applies to PTSD (Stein et al., 2002; True et al., 1993), although data is not robust. The major contribution to the development of PTSD appears to be environmental. The distinction between genetic vulnerability and environment in PTSD is further complicated by the fact that inheritability may also affect the

risk of exposure to trauma (Lyons et al., 1993). In fact, there appears to be a genetic vulnerability for trauma exposure, largely dependant on pre–trauma personality factors (Koenen et al., 2002).

Furthermore, the effect of stressful life events on expression of depressive symptoms is apparently linked to 5–HT transporter gene polymorphism (Caspi et al., 2003). Additionally, the term "environmental" is very broad, and includes events happening before, during and after exposure to trauma. PTSD has even been associated with physical and psychological events occurring during pregnancy (Huizink, Mulder, and Buitelaar, 2004; McCormick et al., 2000; Smythe, McCormick, and Meaney, 1996) and early childhood stress (Teicher et al., 2003). The interaction between genetic vulnerability and environmental stressors highlights the need for an extensive, meticulous collection of personal and family history data as a prerequisite for meaningful neuropathological research.

Stress can trigger or exacerbate the course of almost all mental disorders (Corcoran et al., 2003; Gutman and Nemeroff, 2003). Applying the same rationale used in discussing the potential neuropathological similarities within the stress response spectrum presented above, it is plausible that there may be a neuropathological continuity across psychiatric disorders, corresponding to their overlapping phenomenology (i.e., symptoms of depression, anxiety and psychomotor retardation or agitation are found across disorders) (Harrison, 2002). PTSD is highly comorbid with substance abuse, major depression, panic disorder and generalized anxiety (Kessler et al., 1995). The likelihood of a neuropathological continuity across disorders is supported by comparable findings in brain imaging studies, genetic predisposition and response to similar medications.

CONCLUSION

Among mental disorders, PTSD has a unique advantage for studying the interaction between environment and biology: Triggered by an identifiable event, it provides an opportunity to correlate putative changes in the brain with the development of a maladaptive behavioral pattern. However, a brain repository, perhaps more than other research modalities, relies on brains of older individuals, in most cases obtainable many years after the traumatic event. Neuropathology may therefore not be suitable to document the effects of exposure to acute trauma, if any, as well as the development of cerebral changes that parallel the evolution of PTSD.

Differences in neurobiology between patients with PTSD and resilient individuals may antedate the traumatic event, result from exposure to severe stress, develop gradually from long–term distress or reflect prolonged administration of medication or abuse of illicit substances. The use of neuropathology to study the stress response is complicated by the need to distinguish between the above possibilities. Such interpretation of data requires a comprehensive premorbid evaluation, including detailed psychometric, psychophysiological and neuropsychological assessments as well as laboratory and brain imaging studies. Information obtained from relatives after death would not be sufficient for this.

A complementary approach, recently utilized in a landmark brain imaging study of PTSD (Gilbertson et al., 2002), would be to try and collect postmortem brains of identical twin pairs in which one member was exposed to a severe traumatic event. In some pairs, the exposed twin would suffer from PTSD while in others both twins will be healthy. This design could help determine whether PTSD–related brain abnormalities, if found, precede exposure to trauma, result from it or reflect the accumulative effect of long–term PTSD. In view of the diversity in clinical presentation and nonspecificity of the biological findings in PTSD, associating neuro– and psychopathology will require many years of careful and arduous endeavor.

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